

GUIDELINES FOR DENTAL TREATMENT OF PATIENTS WITH INHERITED BLEEDING DISORDERS

Andrew Brewer

Oral & Maxillofacial Surgery Department
The Royal Infirmary
Glasgow, Scotland

Maria Elvira Correa

Centro de Hematologia e Hemoterapia da Unicamp
Sao Paulo, Brazil

On behalf of

World Federation of Hemophilia Dental Committee

Published by the World Federation of Hemophilia (WFH)

© World Federation of Hemophilia, 2006

The WFH encourages redistribution of its publications for educational purposes by not-for-profit hemophilia organizations. In order to obtain permission to reprint, redistribute, or translate this publication, please contact the Communications Department at the address below.

This publication is accessible from the World Federation of Hemophilia's web site at **www.wfh.org**. Additional copies are also available from the WFH at:

World Federation of Hemophilia
1425 René Lévesque Boulevard West, Suite 1010
Montréal, Québec H3G 1T7
CANADA
Tel. : (514) 875-7944
Fax : (514) 875-8916
E-mail: wfh@wfh.org
Internet: www.wfh.org

The *Treatment of Hemophilia* series is intended to provide general information on the treatment and management of hemophilia. The World Federation of Hemophilia does not engage in the practice of medicine and under no circumstances recommends particular treatment for specific individuals. Dose schedules and other treatment regimes are continually revised and new side effects recognized. WFH makes no representation, express or implied, that drug doses or other treatment recommendations in this publication are correct. For these reasons it is strongly recommended that individuals seek the advice of a medical adviser and/or to consult printed instructions provided by the pharmaceutical company before administering any of the drugs referred to in this monograph.

Statements and opinions expressed here do not necessarily represent the opinions, policies, or recommendations of the World Federation of Hemophilia, its Executive Committee, or its staff.

Treatment of Hemophilia Monographs
Series Editor
Dr. Sam Schulman

Acknowledgements

The WFH is grateful to members of the WFH Dental Committee for their work in developing these guidelines. Thanks also to Dr Richard A. Lipton and Barbara McDonald for their help.

Series editor's note

The monograph adds to two previous WFH monographs on oral and dental care, prophylaxis and treatment (Treatment of Hemophilia Monographs No. 3 and 27). It is written by dentists for dentists and does not provide specific guidelines regarding doses of factor concentrates. Details on that and results from a decade of treatments and oral surgical procedures have been published by Franchini et al (Haemophilia 2005;11:504-9) and may be helpful to read for the hematologist involved in the team.

Table of Contents

Foreword.....	1
Introduction.....	1
Minimizing the use of clotting factor concentrates.....	1
Prevention.....	2
Dental treatment	3
Periodontal treatment	3
Removable prosthodontics.....	3
Orthodontic treatment	3
Restorative procedures	3
Endodontics.....	4
Anesthesia and pain management	4
Surgery	4
1. Treatment plan.....	4
2. Pre-operative period	5
3. Peri-operative period	5
4. Post-operative period.....	5
Post-extraction hemorrhage	5
Fibrin glue	6
Splints.....	6
Management of oral infections	6
1. Dental infections.....	6
2. Periodontal infection.....	7
3. Topical treatment.....	7
Dental emergencies	7
Conclusion.....	7
References	8

Guidelines for Dental Treatment of Patients with Inherited Bleeding Disorders

Dental Committee, World Federation of Hemophilia

Foreword

The dental treatment of patients with inherited bleeding disorders has been widely discussed in the literature with the aim of developing guidelines for common procedures. The majority of guidelines recommend the use of clotting factor replacement therapy before invasive oral surgery and the use of the inferior alveolar nerve block for restorative dental treatment. The dose of clotting factor used varies and this may be due to problems relating to both the availability and cost of factor concentrates in different parts of the world.

Successful protocols are the result of cooperation between hematologists and dentists. These protocols suggest the use of factor concentrate along with the use of local hemostatic techniques, such as suturing, and local measures, such as the use of oxidized cellulose, for example Surgicel® or fibrin glue in conjunction with post-operatively administered antifibrinolytic agents where appropriate. The use of local techniques has resulted in certain minor oral surgery procedures being done with minimal or no coagulation factor replacement.

The purpose of these guidelines is to provide a basis for the development of local protocols for the dental treatment of patients with inherited bleeding disorders.

Introduction

Hemophilia is an X-linked hereditary disorder. Hemophilia A is a deficiency of factor VIII and hemophilia B (Christmas disease) is a deficiency of factor IX. Hemophilia is considered severe when plasma activity is <1 IU/dL (normal range 50-100); moderate if it ranges between 2 and 5 IU/dL, and mild if it is between 6 and 40 IU/dL [1].

The treatment of the patients with either hemophilia A or hemophilia B involves the

replacement of the deficient clotting factors by intravenous infusion to either control or prevent bleeding[2].

Viral inactivation of plasma-derived factor concentrates was introduced in the mid-1980s and the use of recombinant (non-human derived) factor concentrates started in the early 1990s. These measures have reduced, if not removed, the risk of viral transmission with these products. Before this, patients with hemophilia and other bleeding disorders were exposed to human immunodeficiency virus (HIV) and hepatitis C virus (HCV) [3]. The presence of HCV in patients with hemophilia previously treated with non-inactivated concentrates presently ranges from 70% to 90% [4,5]. Recently the potential risk of transmission of vCJD has concerned clinicians although the actual level of risk is difficult to quantify it should not affect routine dental care [6].

A further potential complication of factor replacement therapy is the development of antibodies or inhibitors to factors VIII or IX. Inhibitors usually develop early in a person's treatment [2]. Antibodies to both factor VIII and IX have been found in 8 to 20% of the patients with severe hemophilia A, and in 2.5 to 16% of those with severe hemophilia B [7,8]. The problems associated with the dental management of this group of patients will be discussed in a separate publication.

Minimizing the use of clotting factor concentrates

In certain parts of the world, access to and availability of clotting factor concentrates can be a problem. Treatment guidelines developed in countries where factor concentrates are readily available may not be appropriate in countries where clotting factor concentrates are less available and less affordable. Hemophilia centres in these countries seek to develop guidelines that rely less on systemic hemostatic therapy. The aim of this publication is to

provide guidelines that allow dental treatment to be carried out safely whilst minimizing the use of factor concentrates.

Historically, international guidelines for oral surgery recommended the administration of clotting factor concentrates both before and after surgery. Doses are calculated to increase the level of factor VIII or IX to 50-100 IU/dL for a period of at least seven days [9,10]. Ublansky *et al.* [11] advised an increase of factor VIII or IX to 50% for either regional or infiltration local anesthesia.

The literature describes many successful dental treatment protocols that provide a remarkable reduction in the number of bleeding episodes following oral procedures using oral antifibrinolytic agents, systemic hemostatic replacement therapy, and local hemostatic agents [12-17].

In a WFH monograph by Harrington [18], lower doses (30% of normal) of clotting factor concentrates are recommended for infiltration anesthesia of the lower jaw and periodontal curettage. For more invasive surgical interventions, the recommendation is to increase the factor level from 50-100 IU/dL of normal pre-operatively, and use an oral antifibrinolytic agent pre- and post-operatively.

Sindet-Pedersen [15,17] suggests that the dose of factor replacement therapy can be significantly reduced if used with an oral rinse of an antifibrinolytic agent (tranexamic acid) is used following a dental extraction. He recommends a single dose of factor, in cases of severe hemophilia A elevating the factor VIII level to 10IU/dL. Desmopressin, a synthetic derivative of the hormone vasopressin, has been shown to increase factor VIII level in some patients with mild or moderate forms of hemophilia A or type 1 von Willebrand disease. Unfortunately, not all patients respond so this should be checked before performing any surgical procedure. Its use is well documented in cases of mild and moderate hemophilia A [19-21]. DDAVP releases bound factor VIII and is therefore not used to treat patients with hemophilia B. A report by Ehl *et al.* [22] showing a clinical response to desmopressin in four patients with hemophilia B with baseline factor IX levels of 1.4 to 5% for oral surgery. They report a reduction

in the use for plasma products following treatment.

Fibrin glue is used as a local hemostatic measure in some centres for achieving hemostasis and reducing the needs for clotting factor replacement therapy (see section on page 6).

Prevention

The prevention of dental problems is an essential component of oral care. A successful regimen will reduce the need for treatment and should reduce the number of emergency visits.

Dental prevention depends on a number of different factors. Some of these may not be available in developing countries but are included to demonstrate the ideal situation.

- Brushing twice daily with a fluoride toothpaste.
 - 1,000-ppm fluoride toothpaste for children under 7 years of age.
 - 1,400-ppm fluoride toothpaste for people over 7 years of age.

The use of fluoride toothpaste depends on the fluoride concentration in the water supply as well as the use of additional fluoride supplements. It should not be used if fluoride supplements are taken or if the water supply has a fluoride content of 1 ppm or more.

- The toothbrush should have medium texture bristles because hard bristles can cause abrasion of the teeth and soft bristles are inadequate to remove plaque.
- Interdental cleaning aids, such as floss, tape, and interdental brushes, should be used to prevent the formation of dental caries and periodontal disease.
- Fluoride supplements may be used, but are not recommended if the water supply has a fluoride content of 1 ppm or more. Supplements include:
 - Fluoride drops
 - Fluoride tablets
 - Topical application of fluoride using trays
 - Fluoride mouthrinses which can be used on either a daily or a weekly basis.

- The consumption of foods and drinks with a high sugar or acid content should be limited to mealtimes. Three exposures per day is the recommended maximum. The aim is to ensure that the intake of food and drink does not cause the pH of the oral cavity to fall below the critical level of pH 5.5.
- Artificial sweeteners can be used as an alternative to sugars in food and drinks. Examples are aspartame, sorbitol, acesulfamate, etc.
- Regular dental visits, usually every 6 months, will help identify problems early, reinforce prevention, and emphasize the importance of reducing the intake of food and drink containing high levels of sugar or acid.

The Scottish Intercollegiate Guideline Network has published *Preventing Dental Caries in Children at High Risk*, which includes a quick reference guide, may also be a useful resource [23]. It is available from their website at <http://www.sign.ac.uk/pdf/sign47.pdf>.

Dental treatment

It is essential to prevent accidental damage to the oral mucosa when carrying out any procedure in the mouth. Injury can be avoided by:

Careful use of saliva ejectors;
Careful removal of impressions;
Care in the placement of X-ray films, particularly in the sublingual region;
Protection of soft tissues during restorative treatment by using a rubber dam or applying yellow soft paraffin (vaseline®).

Periodontal treatment

Healthy periodontal tissue is essential to prevent bleeding and tooth loss. If oral hygiene is poor treatment must start as soon as possible after the patient has had a dental examination and treatment plan formulated to prevent additional damage to the periodontal tissues. In cases of severe periodontal disease, it may be necessary to carry out supragingival scaling initially along with oral hygiene education. Subgingival scaling can start as soon as the inflammation has decreased. The treatment may need to be carried out over several visits to prevent excessive

blood loss. In addition, chlorhexidine gluconate mouthwash can be used to control periodontal problems. Antibiotics may be required to help reduce the initial inflammation.

Blood loss of all kinds can be controlled locally with direct pressure or periodontal dressings with or without topical antifibrinolytic agents.

Periodontal surgery in patients with bleeding disorders must always be regarded as a high-risk procedure with a significant risk of blood loss. It should only be considered where conservative treatment has failed and oral hygiene is good. Periodontal surgery can be a greater challenge to hemostasis than a simple extraction. The procedure must be carefully planned and the risks fully explained to the patient.

Removable prosthodontics

Patients with bleeding disorders can be given dentures as long as they are comfortable. If a partial denture is provided it is important that the periodontal health of the remaining teeth is maintained.

Orthodontic treatment

Fixed and removable orthodontic appliances may be used along with regular preventive advice and hygiene therapy. Special care should be taken when treating patients with a severe bleeding disorder to ensure that the gingiva is not damaged when fitting the appliance.

Restorative procedures

Restorative treatment can be undertaken routinely providing care is taken to protect the mucosa. There is a risk of bleeding with the use of matrix bands or wooden wedges. This can be controlled by local means or the application of topical agents. The risks of using local anesthetics and the requirement for prophylaxis are discussed in a later section.

Endodontics

Endodontic treatment is generally low risk for patients with bleeding disorders. If a pulpectomy is indicated, the possibility of the tooth requiring conventional endodontic treatment must also be considered. It is important that the procedure be carried out carefully with the working length of the root canal calculated to ensure that the instruments do not pass through the apex of the root canal. The presence of bleeding in the canal is indicative of pulp tissue remaining in the canal. Sodium hypochlorite should be used for irrigation in all cases, followed by the use of calcium hydroxide paste to control the bleeding. Formaldehyde-derived substances may also be used in cases where there is persistent bleeding or even before the pulpectomy.

Anesthesia and pain management

Dental pain can usually be controlled with a minor analgesic such as paracetamol (acetaminophen). Aspirin should not be used due to its inhibitory affect on platelet aggregation. The use of any non-steroidal anti-inflammatory drug (NSAID) must be discussed beforehand with the patient's hematologist because of their effect on platelet aggregation.

There are no restrictions regarding the type of local anesthetic agent used although those with vasoconstrictors may provide additional local hemostasis. It is important to advise patients and parents of children about the risks of local oral trauma before the anesthetic wears off.

A buccal infiltration can be used without any factor replacement. It will anesthetize all the upper teeth and lower anterior and premolar teeth.

The mandibular molar teeth are usually treated using the inferior alveolar nerve block. This should only be given after raising clotting factor levels by appropriate replacement therapy, as there is a risk of bleeding into the muscles along with potential airway compromise due to a hematoma in the retromolar or pterygoid space. The intraligamentary technique or interosseous technique should be considered instead of the mandibular block. Articaine® has been used as a buccal infiltration to anesthetize the lower molar

teeth. A lingual infiltration also requires appropriate factor replacement since the injection is into an area with a rich plexus of blood vessels and the needle is not adjacent to bone. There is a risk of a significant airway obstruction in the event a bleed [24].

LOCAL ANESTHETIC TECHNIQUES	
NO HEMOSTATIC COVER REQUIRED	HEMOSTATIC COVER REQUIRED
Buccal infiltration	Inferior dental block
Intra-papillary injections	Lingual infiltration
Intraligamentary injections	

Surgery

Surgical treatment, including a simple dental extraction, must be planned to minimize the risk of bleeding, excessive bruising, or hematoma formation. The following points will help prevent problems:

Emergency surgical intervention in dentistry is rarely required as pain can often be controlled without resorting to an unplanned treatment. All treatment plans must be discussed with the hemophilia unit if they involve the use of prophylactic cover.

1. Treatment plan

The treatment plan should be formulated using the following guidelines:

- Conduct a thorough clinical and radiographic examination.
- Identify which treatment may require prophylactic cover. If multiple extractions are required, only one or two teeth should be extracted at the first appointment to ensure that hemostasis can be achieved. It is important to remember the patient's social circumstances (Do they live alone? What are their preferences for treatment) as well as the clinical condition when making this decision.
- Observe all patients for a prolonged period after a dental extraction. This may be for a few

hours for those patients with a mild bleeding tendency whilst those with more severe conditions or a history of prolonged bleeding despite hemostatic cover may require supervision overnight in hospital. [25]

- Discuss treatment requiring the administration of coagulation factor or desmopressin (DDAVP) with the hemophilia unit. They will be responsible for arranging the administration and monitoring of treatment products.
- Discuss the use of local hemostatic agents. This could include the use of oxidized cellulose (Surgicel®) or fibrin glue. Fibrin glue should not normally be used in patients who have never received human-derived blood products or those who are receiving treatment with recombinant factor VIII or IX because of the potential risks of human viral transmission.
- Consider whether to use antibiotics following a dental extraction. This is controversial, but there are a number of anecdotal reports suggesting that their use may prevent a late bleed, which is thought to be due to infection. However, if a patient has an infection before treatment, it should be treated with antibiotics.
- Always carry out treatment as atraumatically as possible.

2. Pre-operative period

- Ensure that the oral cavity is as healthy as possible before any surgical procedure. This can be achieved by arranging treatment with a hygienist to remove as much calculus and plaque as possible. The regular use of an antibacterial mouthwash, for example chlorhexidine, may also help.
- Consider using an antifibrinolytic agent. It may be helpful to start the treatment the day before the surgery. Tranexamic acid (usual adult dose 1 g three times a day) and epsilon aminocaproic acid (EACA) (50 mg/kg four times a day), are the most commonly used drugs. They should be continued for a total of 7 days.

3. Peri-operative period

- Have the patient rinse with chlorhexidine mouthwash for 2 minutes before the administration of the local anesthetic.

- Carry out the extraction out as atraumatically as possible.
- Suture the socket if the gingival margins do not oppose well. Brewer [26] reports a small series where sutures were not used routinely and there was no significant increase in post-extraction hemorrhage. Resorbable and non-resorbable sutures may be used at the operator's discretion. The only problem with non-resorbable sutures is the need for a post-operative visit and the possibility of bleeding when the suture is removed.
- Use local hemostatic measures if indicated. These include the use of oxidized cellulose or fibrin glue (see notes on the use of fibrin glue).
- Use a soft vacuum formed splint to protect the socket if needed.

4. Post-operative period

The patient must be given detailed post-operative instructions:

- No mouth rinsing for 24 hours;
- No smoking for 24 hours;
- Soft diet for 24 hours;
- No strenuous activities for 24 hours;
- Prescribed medication must be taken as instructed;
- Analgesia should be prescribed for use if required;
- Salt-water mouthwashes (1 teaspoon of salt in a glass of warm water) should be used four times a day starting the day after the extraction for 7 days [27];
- Antibacterial mouthwash may be used;
- Emergency contact details must be given to the patient in case of problems.

Post-extraction hemorrhage

Careful pre-operative planning and the use of antifibrinolytic agents will prevent many post-operative problems [28]. However, post-extraction bleeding will occur on occasion. If post-extraction hemorrhage occurs: Contact the hemophilia unit and consider using additional factor concentrate.

Inspect the site of the bleed. If there is any evidence of a tear in the gingiva or other obvious bleeding point this should be treated using local measures as previously described.

Instruct the patient to sit up and bite on a damp gauze swab for at least 10 minutes.

Use a 10% solution of tranexamic acid or EACA to dampen the swab or as a mouthwash if the bleeding is difficult to stop.

Monitor the patient's blood pressure as it may increase due to worry and pain. If the patient has pain, a suitable analgesic should be prescribed whilst if there is no pain a small dose of a benzodiazepine or similar will help to reduce the worry and reduce the blood pressure.

Fibrin glue

In some hemophilia centres, fibrin glue is used as a local hemostatic measure, along with an oral antifibrinolytic agent, to achieve hemostasis and reduce the need for clotting factor replacement therapy. All fibrin glue contains human or animal components, which has made a number of physicians and patients being hesitant to use this treatment particularly for patients who are receiving recombinant factor concentrates or have never received blood products derived from humans.

Fibrin glue mimics the final pathway of coagulation cascade at the point where fibrinogen is converted into fibrin in the presence of thrombin, factor XIII, fibronectin, and ionized calcium. The cascade reaction provokes the cleavage of fibrinogen through thrombin, forming fibrin peptides A and B from each molecule of fibrinogen resulting in the formation of the fibrin monomers. Thrombin itself also activates factor XIII, which in the presence of calcium permits the stabilization of the clot. Fibronectin takes part in the process as well and its inclusion in the adhesive system appears to promote cellular migration and the activation of fibroblasts in the area where the fibrin glue was applied [29-32].

Splints

Soft vacuum-formed splints can be used to provide local protection following a dental extraction or prolonged post-extraction bleed. The following technique is used to construct the splint pre-operatively:

- Take a dental impression before the extraction and cast a model in the laboratory.
- Remove the tooth being extracted from the model.

- Construct a soft vacuum-formed splint to cover the socket completely.
- Keep the splint in place for at least 48 hours before checking the socket. If there is any sign of bleeding it should be replaced and checked every 24 hours.

If the splint is to be used to stop a post-extraction hemorrhage, the impression must be thoroughly cleaned and disinfected before it is transported to the laboratory.

Management of oral infections

Dental infections

Many patients with infections of dental origin are managed without the use of antibiotics but instead by dental extraction or endodontic treatment, for example [33].

Antibiotics are often used to treat an acute bacterial infection. This should be considered for all patients with inherited bleeding disorders since surgical intervention should be avoided if possible. The initial treatment usually starts based on the normal oral pathogens, *Streptococcus viridans*, anaerobic gram-positive cocci and anaerobic gram-negative rods. Antibiotic regimes should cover all of these groups of organisms [34].

Penicillin is a first-line antibiotic used to treat dental infections. It can be taken orally in the form of penicillin V. Metronidazole is extremely effective in treating anaerobes and is often used in combination with penicillin to give good coverage of both the aerobic and anaerobic bacteria present in the oral cavity. The doses of the drugs may vary depending on the availability in different countries but the treatment should continue for 5-7 days.

A number of different formulations of penicillin are available with a broader spectrum of activity. These can be used either alone or in conjunction with metronidazole. However, it is important to remember that if these drugs are ineffective treatment of the infection will become more complicated.

Erythromycin and clindamycin have been prescribed to patients who are allergic to penicillin [33]. These drugs can be used in

conjunction with metronidazole. Erythromycin may be effective in people with penicillin allergies, but it may not be suitable for more severe infections [34].

Clindamycin produces high alveolar concentrations [35], and bactericidal activity is reached with the usual recommended oral dose of 150 mg every 6 hours. In more severe cases it can be given intravenously. It has been reported that clindamycin can cause antibiotic-associated colitis and therefore is often reserved for the treatment of the more serious infections or when penicillin has failed [33,34].

Periodontal infection

Periodontal pockets host a variety of different bacteria, the majority of them being anaerobic. Regular oral hygiene prevents these bacteria from causing gingival inflammation.

In patients with severe gingival inflammation, in particular those who are immune compromised, the use of an antimicrobial agent may be indicated. Metronidazole is considered the drug of choice due to its action against anaerobic organisms. It may be used in conjunction with either penicillin or erythromycin. However, antimicrobial therapy is no substitute for oral hygiene treatment.

Topical treatment

The most common forms of topical treatment involve the use of an antibacterial mouthwash. These have value as an adjunct to hygiene phase treatment. The most common treatments are:

- Chlorhexidine gluconate: Chlorhexidine is available as a mouthwash, spray, and toothgel. It is most commonly used as a twice a day mouthwash with the patient rinsing their mouth with the solution for 30–60 seconds. The toothgel may be used in addition to the mouthwash. chlorhexidine has a tendency to stain teeth so the length of each course of treatment should be limited.
- Povidine-iodine: povidine-iodine is available as a mouthwash and can be used for the treatment of acute periodontal problems. In addition, it may be useful to irrigate the periodontal pockets. It must be used with caution during pregnancy.

Dental emergencies

Dental emergencies can occur at any time; however, it is important to remember that no treatment should be carried out without prior planning as this could result in additional problems.

The most common dental problems are pain due to caries and bleeding from the periodontal tissues. Pain related to caries can usually be treated with either antibiotics or pulpectomy in order to allow time for the planning of the extraction. Bleeding from the periodontal tissues can usually be controlled with antibiotics until an appointment with a hygienist can be arranged.

The management of dental trauma is more complex as it usually involves both the gingiva and the teeth. Local measures will usually control gingival bleeding and temporary splinting can be used for fractured or loose teeth.

With dental trauma, it is important to remember that we are part of the comprehensive hemophilia care team treating these patients. Treatment planning for an emergency requires input from the whole team to reduce the risk of further problems.

Conclusion

The monograph has been written to help healthcare workers develop local guidelines for the management of patients with inherited bleeding disorders. They should be studied in conjunction with the two previously published WFH monographs *Primary Dental Care of Patients with Hemophilia* [18] and *Oral Care for People with Hemophilia or a Hereditary Bleeding Tendency* [36].

We should like to thank the members of the dental committee for their help and support in the development of these guidelines and hope that they help hemophilia healthcare workers throughout the world improve dental care for their patients.

References

1. White GC 2nd, Rosendaal F, Aledort LM, Lusher JM, Rothschild C, Ingerslev J. Factor VIII and Factor IX Subcommittee. Definitions in hemophilia. Recommendation of the scientific subcommittee on factor VIII and factor IX of the scientific and standardization committee of the International Society on Thrombosis and Haemostasis. *Thromb Haemost*, 2001; 85(3):560.
2. Nilsson IM. *Hemophilia*. Stockholm: Pharmacia Plasma Products: 1994.
3. Fried M W. Management of hepatitis C in the hemophilia patient. *Am J Med* 1999; 107(6B):85S-89S.
4. Kumar A, Kulkarni R, Murray DL, *et al*. Serologic markers of viral hepatitis A, B, C and D in patients with hemophilia. *J Med Virol* 1993; 41:205-9.
5. Eyster ME, Diamondstone LS, Lien JM, *et al*. Natural history of hepatitis C virus infection in multitransfused hemophiliacs: effect of coinfection with human immunodeficiency virus. The Multicenter Hemophilia Cohort Study. *J Acquir Immune Defic Syndr Hum Retrovirol* 1993; 6:602-10.
6. Brewer AK and Giangrande, P. Letter to British Dental Journal. *Br Dent J* 2005; 198(4):217.
7. Shapiro SS, Huntin M. Acquired inhibitors to the blood coagulation factors. *Sem Thromb Hemost* 1975; 1:336.
8. Sultan Y, the French Hemophilia Study Group. Prevalence of inhibitors in a population of 3435 hemophilia patients in France. *Thromb Haemost* 1992; 67:600-2.
9. Mulkey TF. Outpatient treatment of hemophiliacs for dental extractions. *J Oral Surg* 1976; 34:428-34.
10. Evans BE. *Cuidado Dental en Hemofilia*. El Tratamiento de la Hemofilia, Federación Mundial de la Hemofilia. Berkeley, California: Cutter Laboratories, Inc, 1981.
11. Ublansky JH. Comprehensive dental care for children with bleeding disorders – a dentist's perspective. *J Can Dent Assoc* 1992, 58(2);111-14.
12. Larsen PE. Dental Management of the Patient with Hemophilia. (Letter) *Oral Surg Oral Med Oral Pathol* 1989; 67(5):632-33.
13. Sindet-Pedersen S, Ingerslev J, Ramström G *et al*. Management of oral bleeding in haemophilic patients. *Lancet* 1988; 3:566.
14. Sindet-Pedersen S. Haemostasis in oral surgery – the possible pathogenetic implications of oral fibrinolysis on bleeding. Experimental and clinical studies of the haemostatic balance in the oral cavity, with particular reference to patients with acquired and congenital defects of the coagulation system. *Dan Med Bull* 1991; 38(6):427-43.
15. Sindet-Pedersen S; Gram J, and Jespersen J. The possible role of oral epithelial cells in tissue-type plasminogen activator-related fibrinolysis in human saliva. *J Dent Res* 1990; 69(6):1283-86.
16. Sindet-Pedersen S; Stenbjerg S, Ingerslev J and Karring T. Surgical treatment of severe periodontitis in a haemophilic patient with inhibitors to factor VIII. Report of a case. *J Clin Periodontol* 1988; 15:636-38.
17. Sindet-Pedersen; Gram J and Jespersen J. Characterization of plasminogen activators in unstimulated and stimulated human whole saliva. *J Dent Res* 1987; 66(6):1199-1203.
18. Harrington B. *Primary dental care of patients with haemophilia*. Treatment of Hemophilia Monograph Series. Montreal, Canada: World Federation of Hemophilia, 2004.
19. Mannuci PM, Aberg M, Nilsson IM, Roberteson B. Mechanism of plasminogen activator and factor VIII increase after vasopressin drugs. *Br J Haematol* 1975; 30:81-3.
20. Kobrinsky N, Israel ED, Gerrard J *et al*. Shortening of bleeding time by DDAVP in various bleeding disorders. *Lancet* 1984; 1:1144-48.
21. Saulnier J, Marey A, Horellou MH *et al*. Evaluation of desmopressin for dental extraction inpatients with haemostatic disorders. *Oral Surg Oral Med Oral Pathol* 1994; 77(1):6-12.
22. Ehl S; Severin T; Sutor AH. DDAVP (desmopressin; 1-deamino-cys-8-D-arginine-vasopressin) treatment in children with haemophilia. *Br J Haematol* 2000; 111:1260-62.

23. Scottish Intercollegiate Guidelines Network Preventing dental caries in children at high caries risk. Publication number 47. Edinburgh, U.K.: Scottish intercollegiate guidelines network, 2000.
24. Wray D, Lowe GDO, Dagg JH, Felix DH and Scully C. *Textbook of general and oral medicine*. London: Harcourt Brace, Churchill Livingstone, 1999.
25. Brewer AK; Roebuck EM; Donachie M *et al*. Dental management of adult patients with haemophilia and other congenital bleeding disorders. *Haemophilia* 2003; 9:1-5.
26. Brewer AK. Prospective cohort study of extractions carried out on adult patients with haemophilia and other congenital bleeding disorders. Scottish oral and maxillofacial surgeons meeting, October 2005. Edinburgh
27. British National Formulary, March 2006 section 12.3.4. BMA publishing and RPS publishing, London
28. Walsh PN; Rizza CR; Matthews JM *et al*. Epsilon-amino-caproic acid therapy for dental extraction in haemophilia and Christmas disease. *Br J Haematol* 1971; 20:463.
29. Gible JW and Ness PM. Fibrin Glue: the perfect operative sealant? *Transfusion* 1990; 30(8): 741-7.
30. Chabbat J; Tellier M; Porte P *et al*. Properties of a new fibrin glue stable in liquid state. *Thrombosis Res* 1994; 76(6):525-33.
31. Alving BM; Weinstein MJ; Finlayson JS; *et al*. Fibrin sealant: summary of a conference on characteristics and clinical uses. *Transfusion* 1997; 35:783-90.
32. Martinowitz U and Spotnitz W. Fibrin tissue adhesives. *Thromb Haemost* 1997; 78(1):661-6.
33. Gill Y & Scully C. Orofacial odontogenic infections: review of microbiology and current treatment. *Oral Surg Oral Med Oral Pathol* 1990; 70:155-8.
34. Kuriyama T; Karasawa T; Kiyomasa N; *et al*. Bacteriologic features and antimicrobial susceptibility in isolates from orofacial odontogenic infections. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2000; 90:600-8.
35. Baker KA; Fotos PG. The management of odontogenic infections. A rationale for appropriate chemotherapy. *Dent Clin North Am* 1994; 38:689-710.